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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20  
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)  
APR 81 M J TOPPER, M H WEEKS  
USAEHA-75-51-0193-81

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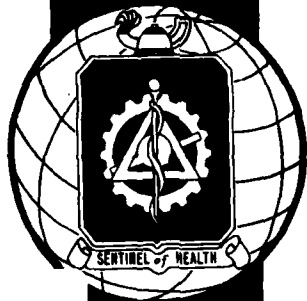
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**UNITED STATES ARMY  
ENVIRONMENTAL HYGIENE  
AGENCY**

**ABERDEEN PROVING GROUND, MD 21010**

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TOPICAL HAZARD EVALUATION PROGRAM  
OF CANDIDATE INSECT REPELLENTS  
AI3-37579 and AI3-37580  
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS  
STUDY NUMBERS 75-51-0193-81 AND 75-51-0194-81



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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 75-51-0193-81 and 75-51-0194-81	2. GOVT ACCESSION NO. AD-A097	3. RECIPIENT'S CATALOG NUMBER 833
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7. AUTHOR(s) Michael J. Topper, CPT, VC Maurice H. Weeks		6. PERFORMING ORG. REPORT NUMBER 75-51-0193-81 & 75-51-0194-81
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18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) USDA Proprietary Chemical      Candidate Repellents AI3-37579      skin irritation AI3-37580      eye irritation Topical Hazard Evaluation      guinea pig sensitization ALD      photochemical irritation		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluations of AI3-37579 and AI3-37580 were performed by means of laboratory animal studies using rats, rabbits and guinea pigs. Chemical AI3-37579 produced a mild primary skin irritation while AI3-37580 produced no primary skin irritation. However, neither chemical demonstrated potential to cause eye or photochemical irritation to sensitize guinea pigs or demonstrate an acute ingestion hazard. It was recommended that AI3-37579 and AI3-37580 be approved for further testings as candidate insect repellents.		

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DEPARTMENT OF THE ARMY  
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY  
ABERDEEN PROVING GROUND, MARYLAND 21010

CPT Topper/jg/AUTOVON  
584-3980

REPLY TO  
ATTENTION OF  
HSE-LT-T/WP

14 APR 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents  
AI3-37579 and AI3-37580, US Department of Agriculture Proprietary  
Chemicals, Study Numbers 75-51-0193-81 and 75-51-0194-81, October  
1978 - January 1981

Executive Secretary  
Armed Forces Pest Management Board  
Forest Glen Section, WRAMC  
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluations of AI3-37579 and AI3-37580 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. Chemical AI3-37579 produced a mild primary skin irritation, while AI3-37580 produced no primary skin irritation. The technical grade chemicals did not cause eye or photo irritation. They did not prove to be skin sensitizers or to be acutely toxic by ingestion. It was recommended that both chemicals be approved for further testing as candidate insect repellents.

FOR THE COMMANDER:

1 Incl  
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*John F. Mazur*  
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REPLY TO  
ATTENTION OF

HSE-LT-T/WP

DEPARTMENT OF THE ARMY  
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY  
ABERDEEN PROVING GROUND, MARYLAND 21010

TOPICAL HAZARD EVALUATION PROGRAM  
OF CANDIDATE INSECT REPELLENTS  
AI3-37579 and AI3-37580  
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS  
STUDY NUMBERS 75-51-0193-81 AND 75-51-0194-81

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man and Animal Research Laboratory, Gainesville, Florida, 13 October 1978.

b. Memorandum of Understanding between the Department of the Army; Office of The Surgeon General; the US Army Health Services Command; the US Army Environmental Hygiene Agency; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration, titled: Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, USAEHA, 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37579 and AI3-37580.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate insect repellents AI3-37579 and AI3-37580, US Department of Agriculture (USDA) Proprietary Chemicals, were conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:\*†

\* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education, and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

TABLE. PRESENTATION OF DATA

<u>Test</u>	<u>Results</u>	<u>Interpretation</u>
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SKIN IRRITATION STUDIES

Rabbits

Single 24-hour application to intact and abraded skin of New Zealand White rabbits.

Chemical AI3-37579 did cause a mild primary irritation of the intact skin and the skin surrounding an abrasion.

AI3-37579 USAEHA Category II (ref Appendix A)

0.5 mL technical grade chemical applied to each of six rabbits.

Chemical AI3-37580 did not cause any irritation of the skin surrounding an abrasion (ref Appendices B and C for details).

AI3-37580 USAEHA Category I (ref Appendix A)

EYE IRRITATION STUDIES

Rabbits

Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.

Chemicals AI3-3759 and AI3-37580 did not cause any irritation to the eyes of rabbits (ref Appendices D and E for details).

Both chemicals USAEHA Category A (ref Appendix A)

APPROXIMATE LETHAL DOSE (ALD)

Oral

Rats (male)-no diluent

AI3-37579 ALD = 6500  
AI3-37580 ALD = 9700

Neither chemical presents a lethal hazard from accidental ingestion.

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

Test	Results	Interpretation
------	---------	----------------

PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single 0.05 mL application of a 25 percent (w/v) solution of each chemical and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.

Neither chemical caused a photochemical irritation reaction under test conditions (ref Appendices F and G for details).

Neither chemical caused a photochemical irritation reaction under test conditions and they are not expected to cause a photochemical irritation in humans.

Control

Following UV exposures of the rabbits, 0.05 mL of test chemical, positive control, and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.

Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

Test	Results	Interpretation
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SENSITIZATION STUDIES

Guinea Pigs (Male)

Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of test chemicals or of dinitrochlorobenzene (DNCB)\* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks' rest, they were challenged with ID injections of each test chemical.

Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks' rest, they were challenged with ID injections of DNCB.

Challenge doses of test chemicals did not produce a sensitization reaction (ref Appendices H and I for details).

Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.

Chemicals AI3-37579 and AI3-37580 did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.

DBCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

\* A known skin sensitizer.



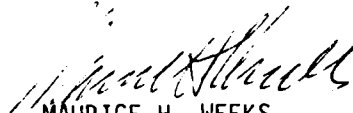
Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

5. CONCLUSION. Technical grade chemicals AI3-37579 and AI3-27580 did not cause any eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard. Chemical AI3-37579 did produce a mild primary skin irritation, while AI3-37580 did not.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37679 and AI3-37580 be approved for further testing as candidate insect repellents.

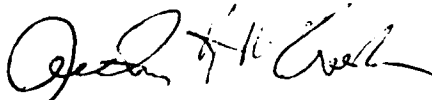


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TOPICAL HAZARD EVALUATION PROGRAM  
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING  
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX B

CHEMICAL: AI3-37579, USDA Proprietary Chemical		USAEHA STUDY NO: 75-51-0193-81									
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS		USAEHA TOXICITY CATEGORY II									
		CONDITIONS - 0.5 mL technical grade chemical applied to intact and abraded skin.									
	Time of Observation Hours	Response Rabbit No.									
		103	104	105	106	107	108	Mean Score			
<u>Erythema &amp; Eschar</u>											
Intact Skin	24	1		0		2		0.50			
Intact Skin	72	0		0		0					
Abraded Skin	24			0		0	1	0.16			
Abraded Skin	72			0		0	0				
							Subtotal	0.66			
<u>Edema Formation</u>											
Intact Skin	24	0		0		1		0.16			
Intact Skin	72	0		0		0		0			
Abraded Skin	24			0		0	0	0			
Abraded Skin	72			0		0	0	0			
							Subtotal	0.16			
							Total Avg	0.41			

HSE-LT Form 39-2, 1 Jun 80

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX C

CHEMICAL: AI3-37580, USDA Proprietary Chemical										USAEHA STUDY NO. 75-51-0194-81											
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS				USAEHA TOXICITY CATEGORY  I				CONDITIONS - 0.5 mL technical grade chemical applied to intact and abraded skin.													
	Time of Observation Hours	Response Rabbit No.								Mean Score	Comments										
		Rabbit No.																			
		103	104	105	106	107	108														
<u>Erythema &amp; Eschar</u>																					
Intact Skin	24		0		1				1		0.33										
Intact Skin	72		0		0				0												
Abraded Skin	24	1		1				2			0.67										
Abraded Skin	72	0		0				0			1.00										
									Subtotal												
<u>Edema Formation</u>																					
Intact Skin	24		0		0				0												
Intact Skin	72		0		0				0												
Abraded Skin	24	0		0				2			0.33										
Abraded Skin	72	0		0				0													
									Subtotal		0.33										
									Total Avg		0.66										

HSE-LT Form 39-2, 1 Jun 80

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX D

CHEMICAL: AI3-37579, USDA Proprietary Chemical			USAEHA STUDY NO. 75-51-0193-81						
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS		USAEHA TOXICITY CATEGORY		CONDITIONS - Single 24-hr application of 0.1 mL technical grade chemical to one eye of each of six rabbits.					
		A							
Time of Reading Hrs-Days	Structure	Scores						Score	Comments
		Rabbit No.							
		1	2	3	4	5	6		
24	cornea iris conjunctivae	827 0 0 0	828 5 0 2	829 0 0 0	830 0 0 0	831 0 0 0	706 0 0 4	5 0 6	
48	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	
72	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	
7-days	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX E

CHEMICAL: A13-37580, USDA Proprietary Chemical										USAEHA STUDY NO. 75-51-0194-81									
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS					USAEHA TOXICITY CATEGORY  A					CONDITIONS - Single 24-hr application of 0.1 mL technical grade chemical to one eye of six rabbits.									
Time of Reading Hrs-Days	Structure	Scores Rabbit No.								Score	Comments								
		19	20	21	22	23	24												
24	cornea iris conjunctivae	0 0 0	0 0 2	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 2										
48	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0										
72	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0										
7-days	cornea iris conjunctivae																		

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX F  
PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

CHEMICAL: AI3-37579, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0193-81						
COMMENTS:								
PROCEDURE: 0.05 mL of a 25 percent solution of chemical and of a 10 percent solution of oil of Bergamot in 95 percent ethanol applied to intact skin of six rabbits. Rabbits were exposed to UV light for 30 minutes.								
MEAN SKIN IRRITATION SCORE								
Observation Time	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	7	5	6	5	20	19	8	5
48 Hours	10	9	7	5	19	22	10	5
72 Hours	8	6	6	3	13	14	1	0
TOTAL	25	20	19	13	52	55	19	10
Mean Irritant Responses	1.39	1.11	1.06	0.72	2.89	3.06	1.06	0.56
Net Score	Erythema 0.33	Edema 0.39	Erythema 1.83	Edema 2.50				

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX G

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

CHEMICAL: AI3-37580, USDA Proprietary Chemical				USAEHA STUDY NO. 75-51-0194-81				
COMMENTS:								
PROCEDURE: 0.05 mL of a 25 percent of chemical and of a 10 percent solution of oil of Bergamct in 95 percent ethanol applied to intact skin of six rabbits. Rabbits were exposed to UV light for 30 minutes.								
	MEAN SKIN IRRITATION SCORE							
Observation Time	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	8	2	9	3	21	22	13	9
48 Hours	8	2	10	5	21	19	11	5
72 Hours	10	1	10	2	19	11	7	1
TOTAL	26	5	29	10	61	52	31	15
Mean Irritant Responses	1.44	0.28	1.61	0.56	3.39	2.89	1.72	0.83
Net Score	Erythema 0.17		Edema 0.28		Erythema 1.67		Edema 2.06	



Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX H

CHEMICAL: AI3-37579, USDA Proprietary Chemical		USAEHA STUDY NO. 75-51-0193-81			
<p>GUINEA PIG SENSITIZATION</p> <p>MALE</p> <p>HARTLEY STRAIN</p> <p>Substance: AI3-37579</p> <p>Identify: USDA Proprietary Chemical</p> <p>Positive Control: Dinitrochlorobenzene</p>					
Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores		Comments
	Initial	Final	Diluent Initial	Test Compound Initial	
Test Compound	439	603	0	6.60	5.30
Positive Control	441	601	0	10.4	344
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores		Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing
	Initial	Final	Diluent Initial	Test Compound Initial	
Test Compound	-	-	-	3.20	4.20
Positive Control	-	-	-	6.60	260

Study Nos. 75-51-0193-81 and 75-51-0194-81, Oct 78 - Jan 81

APPENDIX I

CHEMICAL: A13-37580, USDA Proprietary Chemical												USAEHA CONTROL NO. 75-51-0194-81											
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN												Substance: A13-37580 Identify: USDA Proprietary Chemical Positive Control: Dinitrochlorobenzene											
Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores						Comments														
	Initial	Final	Diluent		Test Compound		Test Compound																
Test Compound	418	576	Initial	0	Final	0	Initial	1.7	Final	3.8													
Positive Control	441	601	Initial	0	Final	0	Initial	10.4	Final	344													
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores																				
	Initial	Final	Diluent		Test Compound		Test Compound																
Test Compound	-	-	Initial	0	Final	0	Initial	0	Final	1.6													
Positive Control	-	-	Initial	0	Final	0	Initial	6.60	Final	260													
												Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing											

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